

# Glucose variability does not contribute to the development of peripheral and autonomic neuropathy in type 1 diabetes: data from the DCCT

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## Abbreviations

EMG Electromyography  
MAGE Mean amplitude of glycaemic excursions

*To the Editor:* While it is suggested that, in addition to hyperglycaemia, glucose variability can contribute to the severity and development of diabetic neuropathy [1], it is not related to the development of retinopathy and nephropathy in type 1 diabetes [1, 2]. To determine any additional effect of glucose variability—above that assessed by HbA<sub>1c</sub> and mean glucose—on peripheral and autonomic diabetic neuropathy, we used the datasets collected during the DCCT (available at [www.gcrc.med.umn.edu/gcrc/downloads/dcct.html](http://www.gcrc.med.umn.edu/gcrc/downloads/dcct.html), accessed 23–27 January 2009) [3].

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We studied the effect of glucose variability on the main neurological endpoint of the DCCT, i.e. confirmed clinical neuropathy, and on the DCCT-defined secondary endpoints separately: clinical neuropathy, abnormal nerve conduction studies, and abnormal autonomic function [4]. In addition, we determined its effect on the subvariables median motor F-wave latency, sural amplitude, sensory signs and beat-to-beat heart-rate variation (with Valsalva ratio <1.5), as these variables tend to be the first affected by diabetes. We included only data from baseline to 4 years (autonomic function data) or 5 years of follow-up in the analyses as more than 50% of the patients did not have records of glucose data after 5 years of follow-up.

We assessed glycaemic variables from seven-point blood glucose profiles collected every 3 months. We included all glucose profiles with five observations or more during the 24 h period, extrapolating missing values from the surrounding points [5]. Mean blood glucose was calculated by the AUC using the trapezoidal rule [6]. Variability of blood glucose (within-day SD) was calculated as the SD of daily blood glucose around the mean from each quarterly visit and the mean amplitude of glycaemic excursions (MAGE) [7]. Last, we calculated the mean SD from individual glucose data transformed to a symmetric distribution according to Kovatchev [8]. Glucose variability from baseline to 4 or 5 years was assessed as the mean SD and mean MAGE from the first quarter to the 16th or 20th quarter of follow-up, respectively.

The main characteristics of the patients in the group analysed for confirmed clinical neuropathy are listed in Table 1. Of the 1,441 patients in total, 1,160 were included in this specific analysis. Ninety-two patients were excluded from the analysis because they had a positive score at baseline and 189 patients had missing data on confirmed clinical neuropathy at baseline ( $n=3$ ) or at 5 years ( $n=186$ ).

**Table 1** Patient characteristics in the group analysed for confirmed clinical neuropathy

Characteristic	Confirmed clinical neuropathy (5 years)		<i>p</i> value
	Yes ( <i>n</i> =108)	No ( <i>n</i> =1,052)	
Age at baseline (years)	28.28 (6.77)	26.40 (7.10)	0.008
Male sex, <i>n</i> (%)	52 (48)	533 (53)	0.38
Diabetes duration at baseline (months)	79.59 (45.62)	68.60 (49.79)	0.02
Conventional treatment, <i>n</i> (%)	80 (74)	517 (49)	<0.001
Primary prevention cohort, <i>n</i> (%)	35 (32)	503 (48)	0.002
HbA <sub>1c</sub> (%)	9.10 (1.58)	8.08 (1.43)	<0.001
Mean glucose (mmol/l)	13.51 (3.33)	11.52 (3.78)	<0.001
MAGE (mmol/l)	8.00 (1.96)	7.55 (1.90)	0.02
SD	4.24 (0.89)	4.05 (0.93)	0.04
SD TF	0.75 (0.17)	0.81 (0.16)	<0.001

Data are means (SD), unless stated otherwise

For this analysis patients with a positive or missing score for confirmed clinical neuropathy at baseline were excluded (neuropathy *n*=92; missing *n*=3)

Patients with a missing score at 5 years are also excluded from the analysis (*n*=186)

*p* values are comparisons between groups (independent samples *t* test)

SD TF, standard deviation obtained from glucose data transformed according to Kovatchev et al.: transformed blood glucose =  $1.794 \times ([\log\{BG\}]^{1.026} - 1.861)$ , where BG is blood glucose in mmol/l [8]

The numbers of participants with data analysed in the other specific neuropathy groups are listed in Table 2. Patients with a positive baseline score on the neuropathy variable studied were excluded from analysis.

Logistic regression analysis adjusted for age (years), sex, disease duration (years), randomised treatment (conventional versus intensive) and prevention cohort (primary versus secondary), showed no effect of glucose variability,

**Table 2** Binary logistic regression analysis relating the effect of different glycaemic variables to neurological complications, as defined by the DCCT

Model	Confirmed clinical neuropathy <sup>a</sup> <i>n</i> =108/1,160 <sup>c</sup>		Clinical neuropathy <sup>a</sup> <i>n</i> =148/1,113 <sup>c</sup>		Autonomic neuropathy <sup>b</sup> <i>n</i> =79/1,258 <sup>c</sup>		Abnormal nerve conduction <sup>a</sup> <i>n</i> =207/813 <sup>c</sup>	
	OR (95% CI)	<i>p</i> value	OR (95% CI)	<i>p</i> value	OR (95% CI)	<i>p</i> value	OR (95% CI)	<i>p</i> value
HbA <sub>1c</sub>	1.64 (1.37–1.95)	<0.001	1.40 (1.20–1.64)	<0.001	1.51 (1.23–1.85)	<0.001	1.62 (1.39–1.90)	<0.001
AUC	1.17 (1.09–1.26)	<0.001	1.13 (1.05–1.21)	0.001	1.15 (1.05–1.26)	0.003	1.15 (1.07–1.23)	<0.001
SD	1.07 (0.83–1.35)	0.67	0.95 (0.77–1.18)	0.66	1.30 (0.99–1.70)	0.06	1.17 (0.96–1.42)	0.12
SD (HbA <sub>1c</sub> )	0.86 (0.67–1.10)	0.24	0.82 (0.66–1.03)	0.08	1.08 (0.82–1.44)	0.58	0.94 (0.75–1.14)	0.46
SD (AUC)	0.85 (0.65–1.10)	0.21	0.78 (0.61–0.99)	0.04	1.09 (0.80–1.48)	0.59	0.95 (0.76–1.19)	0.68
MAGE	1.06 (0.96–1.20)	0.23	1.01 (0.91–1.11)	0.90	1.16 (1.03–1.30)	0.01	1.07 (0.98–1.17)	0.14
MAGE (HbA <sub>1c</sub> )	1.00 (0.89–1.12)	0.95	0.96 (0.86–1.06)	0.37	1.09 (0.96–1.23)	0.18	0.98 (0.90–10.8)	0.74
MAGE (AUC)	1.00 (0.88–1.12)	0.93	0.94 (0.85–1.05)	0.29	1.10 (0.97–1.25)	0.13	1.00 (0.91–1.10)	0.93
SD TF	0.14 (0.04–0.52)	0.003	0.15 (0.05–0.48)	0.001	0.63 (0.13–3.07)	0.57	0.16 (0.06–0.47)	0.001
SD TF (HbA <sub>1c</sub> )	0.36 (0.09–1.37)	0.13	0.25 (0.07–0.86)	0.03	1.42 (0.26–7.71)	0.68	0.62 (0.20–1.87)	0.39
SD TF (AUC)	0.33 (0.08–1.39)	0.13	0.26 (0.08–0.87)	0.03	1.27 (0.25–6.29)	0.77	0.61 (0.19–1.94)	0.40

SD (HbA<sub>1c</sub>), SD (AUC), MAGE (HbA<sub>1c</sub>), MAGE (AUC), SD TF (HbA<sub>1c</sub>) and SD TF (AUC) are six distinct models denoting additional adjustment for (HbA<sub>1c</sub>) or (AUC)

All models were adjusted for baseline covariates (sex, age, disease duration, prevention cohort, randomised treatment)

HbA<sub>1c</sub>, AUC, SD, MAGE and SD TF represent means from quarterly visits: <sup>a</sup> 1–20; <sup>b</sup> 1–16

<sup>c</sup> Patients with a positive neuropathy score at 5 years/complete analysis group per variable

SD TF, standard deviation obtained from glucose data transformed according to Kovatchev et al.: transformed blood glucose =  $1.794 \times ([\log\{BG\}]^{1.026} - 1.861)$ , where BG is blood glucose in mmol/l [8]

computed as the mean SD and mean MAGE from the seven point glucose profiles from quarterly visits 1–20 (first 5 years), on confirmed clinical neuropathy, clinical neuropathy alone or nerve conduction abnormalities (Table 2). Dividing the variables in quartiles and performing the analyses per randomisation group did not change the outcome (data not shown).

No effect of glycaemic variability on clinical neuropathy was seen, with the exception of a small protective effect of the SD adjusted for AUC (Table 2). In addition, no effect of glycaemic variability was seen on the incidence of sensory signs (SD OR 1.00, 95% CI 0.82–1.22,  $p=0.99$ ; MAGE OR 1.02, 95% CI 0.93–1.12,  $p=0.69$ ) as well as in separate analysis of the F-wave latency of the median nerve (SD OR 1.12, 95% CI 0.84–1.49,  $p=0.44$ ; MAGE OR 1.03, 95% CI 0.90–1.17,  $p=0.67$ ) and the amplitude of the sural nerve (SD OR 1.27, 95% CI 1.00–1.60,  $p=0.05$ ; MAGE OR 1.05, 95% CI 0.95–1.17,  $p=0.34$ ). Glycaemic variability seemed to have an effect on autonomic neuropathy, but this effect disappeared when adjusting the model for HbA<sub>1c</sub> or AUC (Table 2). Analysing both randomisation groups separately also did not reveal a relation over HbA<sub>1c</sub> (data not shown). Separate examination of the three autonomic function variables showed that only for beat-to-beat heart rate variation during a Valsalva manoeuvre did the effect remain significant when adjusting for mean glucose (SD OR 2.64, 95% CI 1.17–5.94,  $p=0.02$ ; MAGE OR 1.42, 95% CI 1.07–1.90,  $p=0.02$ ), but not when adjusting for HbA<sub>1c</sub> (SD OR 1.84, 95% CI 0.90–3.76,  $p=0.09$ ; MAGE OR 1.30, 95% CI 0.98–1.72,  $p=0.07$ ). There was no effect of glycaemic variability on beat-to-beat heart-rate variation during deep breathing and postural blood pressure testing (data not shown). Transformation of the individual glucose data according to Kovatchev [8] did not alter the results (Table 2).

These results are in line with earlier analysis of DCCT data describing no influence of glycaemic variability on the development or progression of retinopathy and nephropathy [2]. Bragd and colleagues found that glucose variability (SD) was a borderline predictor of the incidence of peripheral neuropathy in 100 patients with type 1 diabetes and with a follow-up period of 11 years ( $p=0.07$ ; HR 1.73, range 0.94–3.19) [1]. Peripheral neuropathy in their study was defined as sensory neuropathy, as indicated by monofilament testing and an abnormal electromyography (EMG) and/or vibration test. This same study showed a significant relationship between SD and the prevalence of peripheral neuropathy ( $p=0.03$ ; OR 2.34, range 1.06–5.20), perhaps suggesting that the nervous system might be particularly susceptible to glycaemic fluctuations [1].

What strengthens our results is that we did not find a relationship between glucose variability and sensory signs

or median motor F-wave latency and sural amplitude, the earliest indicators of diabetic neuropathy. As diabetic neuropathy is mostly a small-fibre disease, sensory signs are usually the presenting sign of the disease and they are a stable and reliable measure of disease status or progression [9]. Although EMG studies measure large-fibre function, median motor F-wave latency and sural amplitude are the most sensitive of all EMG measures to detect diabetic neuropathy [10, 11].

A limitation of this study is that the variables are calculated from seven point glucose curves by self-monitoring. Continuous glucose monitoring might detect fluctuations occurring between two measurements that would be missed by self-monitoring of blood glucose. Another difficulty is that the neuropathy variables were infrequently scored. Possibly the DCCT/Epidemiology of Diabetes Interventions and Complications (EDIC) follow-up will provide more endpoints as the same neuropathy variables assessed in the DCCT are measured in years 13 or 14 of its follow-up (2007–2008; [www.niddkrepository.org](http://www.niddkrepository.org), accessed 23–27 January 2009). These data have not yet been released.

In conclusion, glucose variability was not a risk factor separate from HbA<sub>1c</sub> or mean glucose in the development of diabetic peripheral neuropathy in the DCCT.

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